UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,562	01/26/2001	William J. Curatolo	PC9674AJTJ	8513

7590 12/26/2006

Gregg C. Benson
Pfizer Inc.
Patent Department, MS 4159
Eastern Point Road
Groton, CT 06340

EXAMINER	
FUBARA, BLESSING M	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/26/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/770,562	CURATOLO ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 1017*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,15,17,22,23,26,28-38,49-51 and 53-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,15,17,22,23,26,28-38,49-51 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of IDS filed 11/01/06, request for extension of time, amendment, remarks, and declaration by Dr. Scott B. McCray, all filed 10/17/06. Claims 5-7, 10, 11, 13, 24, 25, 39, 41-43, 45, 47 and 52 are canceled. Claims 1, 4, 15, 17, 22, 23, 26, 28-38, 49-51 and new claims 53-56 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 4, 15, 17, 22, 23, 26, 28-38, 49-51 and 53-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The specification at paragraphs [0020] and [0056] indicate that all the compositions have residual solvent. Therefore, excluding residual solvent from the composition by amendment, introduces compositions that are new to the instant invention.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4, 15, 17, 22, 23 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigoshi et al. (US 6,254,889 provided by applicant on form 1449).

Kigoshi discloses solid dispersion (abstract) obtained by spray drying (column 4, lines 57 and 58) and the solid dispersion comprises polymers such as the celluloses (for example hydroxypropylmethyl cellulose acetate succinate (column 3, lines 26-49) and xanthine derivative (Table 1). The polymer is present at 5-23% with a preferred amount of 11-15% (column 4, lines 53-56) and the active agent is present at 1-50% with a preferred amount of 3-10% (column 3, lines 21 and 22). The percent drug with respect to the polymer is calculated to range from about 21% to 40% at the preferred range and this amounts touches points within the claimed range in percent of about 71% to about 5%. Claim 1 (a) and (b) and claims 53-56 recite the properties of the composition, and this property is inherent to the composition of Kigoshi.

Kigoshi lists a number of polymers for use with the xanthine derivative and any of the listed would be suitable in the composition. It would have been obvious to one of ordinary skill in the art at the time the invention was mad to prepare the solid dispersion of Kigoshi where the polymer is at 5-23% with a preferred amount of 11-15% and the active agent at 1-50% with a preferred amount of 3-10%. One having ordinary skill in the art would have been motivated to

use any of the listed polymers of which hydroxypropylmethyl cellulose acetate succinate is one and expect that the solubility of the xanthine derivative is enhanced/improved.

5. Claims 1, 4, 15, 17, 22, 49-51 and 53-56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993).

Yamaguchi studies the solubility of solid dispersions of 4-0-(4-methoxmhenyllacetyltylosin (MAT) in carboxymethylethylcellulose (CMEC) or hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT®) and using the solid dispersions an increase of AUC and Cmax of greater than 2.5 fold was observed achieved (abstract). Yamaguchi prepares solid dispersions of MAT in CMEC, AQOAT or EC (ethylcellulose) by spray drying (item # 2 of page 2); the solubility of crystalline MAT is determined to be 0.002 at pH 6.8 (item 1 of page 4 and Table 1). In Figure 2 and at pH 4.0, Yamaguchi shows solid dispersions of MAT and CMEC or AQOAT in a ratio of 10:1 and concentration of the MAT in a use environment from AQOAT carrier matrix is about 650 μg and the concentration of amorphous MAT without a polymer in a use environment is about 220 μg; the ratio of the MAT from the AQOAT matrix to a control, such as the one without a polymer is at least greater than 1.5 and specifically about 2.95 (see page 5 and data extrapolated from Figure 2). Although, Yamaguchi exemplifies the dissolution studies with CMEC, the Yamaguchi reference also discloses MAT with AQOAT as is seen in the abstract, pages 2 (last line) and 5, and Figure 2. MAT bulk powder is used in the study in the preparation of the solid dispersion (page 2, item #1) and powder reads on amorphous. The aqueous solubility ratio is an inherent property of a drug and since no specific drug is recited in claims 1 and 15, the prior art renders claim 53 obvious or meets claim 53.

Yamaguchi describes oral administration, fed state (i.e. "withholding food from the beagles from the night before the study") and measuring of blood concentration (page 4, item # 7 and page 10, item # 4), which description confers the implication of gastrointestinal tract environment and thus, this aspect of the disclosure reads on gastrointestinal tract use environment. Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion. Specifically, paragraph 2, page 2 of translation states " MAT (100 g) and 50 g, 20 g, 10 g or 5 g of CMEC were dissolved in 300 ml, of a 1:1 solvent mixture of methylene chloride and ethanol, then spray-dried (SD-1; Tokyo Rikakikai) at an inlet temperature of 120 °C to form a powder. **Preparation was similarly carried out using AQOAT®** or EC as the carrier" (paragraph 2 of the translation). Thus drug: polymer ratios of from 2:1, 5:1, 10:1 and 20:1 are disclosed.

The difference between Yamaguchi and the instant claims after the current amendment is that Yamaguchi discloses ratios of 2:1, 5:1, 10:1 and 20:1 for the drug to polymer while the instant claims disclose a ratio of 1:0.4 to 1:20. The claimed ratio goes through a point of 1:1 at least, and from the claimed range, it appears any of those ratios of drug to polymer would work in the claimed invention. There is also no demonstration in applicant's specification that any of those specific ratios provide unexpected results to the claimed composition. Yamaguchi does not disclose any amount of residual solvent that may be present or not present after the spray drying process. While the ratio of the drug to polymer in Yamaguchi is increased upward from 2:1, 5:1, 10:1 and 20:1, it is examiner's position a ratio of 2:1 is not drastically very far different

from the claimed ratio where on of the points is 1:1. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition of solid amorphous dispersion according to Yamaguchi where the drug to polymer is in a ratio of 2:1. One having ordinary skill in the art would have been motivated to use various ratios of the drug to polymer, including 1:1 and 2:1 and 1:2 with the expectation of increasing the solubility and bioavailability of MAT, which is an objective of Yamaguchi. In the absence of a factual showing, specifically indicating that the claimed spray dried dispersion having a drug:polymer ratio of 1:0.4 to 1:20 provides unexpected results over the spray dried dispersion of the prior art having a drug : polymer ratio of 2:1, the claimed composition is not inventive over the prior art.

Response to Arguments

6. Applicant's arguments filed 10/17/06 have been fully considered but they are not persuasive.

Applicant argues that a) Yamaguchi does not anticipate the claims and that the claims are novel over Yamaguchi; b) that Yamaguchi discloses a ratio of 10:1, which is a drug loading of 91% and which differs from the inventive ratio of 1:0.4, which is a drug loading of 71%; therefore applicant argues that the claimed invention is distinguished over Yamaguchi in view of the ratio of drug to polymer, c) that Yamaguchi does not "unequivocally disclose solid dispersions comprising AQOAT and MAT in the same ratios reefing to the exact phrase used in Yamaguchi as "preparation was similarly carried out using AQOAT or EC as the carrier." d) That Yamaguchi prepares solid dispersions of MAT/CMEC having ratios 10:5 to 10:20 at page 5, lines 4-10 and applicant contends that CMEC modifies the dissolution characteristics of MAT better than AQOAT, e)

applicant summarizes the drug/polymer ratios in the Table on page 7 of the remarks and f) applicant concludes that Yamaguchi teaches away from using drug:polymer ratios of 10:2.5 and 10:5, which corresponds to drug loads of 80% and 67% respectively. Rather, applicant argues that Yamaguchi discloses drug loads at 91% and 95% for drug/polymer ratios of 10:1 and 10:0.5 respectively.

Response:

The claim 1 is a product claim. The prior art discloses solid amorphous dispersion, Yamaguchi prepares the solid dispersion by spray drying and applicants form the molecular dispersion by spray drying. Thus the dispersion of Yamaguchi formed by spray drying is molecularly dispersed.

Regarding a), examiner agrees with the applicant that Yamaguchi does not anticipate the claims. However, Yamaguchi renders the designated claims obvious as described in the rejection.

Regarding b and c) and the drug/polymer ratios, Yamaguchi discloses drug polymer ratios of 2:1, 5:1, 10:1 and 20:1 and the section quoted by applicant as stating "preparation was similarly carried out using AQOAT or EC as the carrier" does not limit the disclosed ratios to CMEC, instead as the phrase states, Yamaguchi is describing that the AQOAT and EC can be similarly used in those ratios with MAT. There is no disclosure in Yamaguchi that limits those ratios to CMEC. Furthermore, the claimed ratio of drug to polymer is between 1:0.4 and 1:20 and a ratio of 1:2 touches one of the points within that range, and this ratio is rendered obvious by Yamaguchi's ratio of 2:1. There is no demonstration that a 1:2 ratio is inventive over a 2:1

ratio. Further, a consideration of a 2:1 ratio translates into a drug loading of about 67%, which falls within applicants argued drug-loading % in the remarks at the first full paragraph at page 9.

Regarding d), the issue is not whether CMEC is better at dissolving MAT, but whether AQOAT is used to dissolve MAT at a drug/polymer ratio of 2:1. Yes, Yamaguchi discloses the use of AQOAT with MAT at a drug polymer ratio of 2:1 (see paragraph 2 of Yamaguchi).

Regarding e), applicant's summary of the drug/polymer ratio ignores Yamaguchi's disclosure at paragraph 2. Therefore, applicant's summarized ratios are not representative of Yamaguchi teachings.

Regarding f), Yamaguchi does not teach away from using a 67% drug loads but instead a ratio of drug to polymer of 2:1 is approximately 67%.

7. Claims 1, 7, 15, 23, 26, 38, 49-51 and 54-56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593).

Miyajima discloses a pharmaceutical composition that comprises 5-(5,5-dimethyl-1,3,2- dioxaphosphorinane-2-yl)-l,4-dihydro-2,6-dimethyl-4- (3- itrophenyl)-3-pyridine carboxylic acid 2-(phenylmethyl)amino) ethyl ester P-oxide hydrochloride-thanol (NZ-105) and hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT) in a 1:1 ratio (abstract) and column 4, lines 6-8 discloses NZ-105/HPMCAS composition where the amount of the HPMCAS is 1-7 parts by weight per unit of NZ-105. Miyajima's composition further comprises filers, binders, lubricants and disintegrants (column 4, lines 22-47). Miyajima's composition is formulated as powders, granules, tablets, capsules or pills (column 4, lines 16-21). Powder or

particles of NZ-105 and HPMCAS are produced by vacuum drying, spray drying or freeze-drying (column 3, lines 55-6%. While nicardipine and nifedipine are disclosed by Miyajima in the background section as well known 1,4-dihydropyridine-type compounds that are poorly soluble in water and can be prepared as amorphous formulations, the nicardipine and nifedipine are different compounds from the compounds recited in instant claims 29, 30, 32, 34 and 36. Instant claim 37 recites nifedipine as a drug. Examples 1-4 of Miyajima disclose NZ-105/HPMCAS composition where the ratio of the NZ-105 to the HPMCAS is 1:3. Miyajima is silent with respect to the solubility of the drug NZ-105 in a use environment or oral administration or administration to a fasted animal. However, the solubility of the drug is an inherent property of a drug and would appear to be an inherent property of the NZ-105/HPMCAS compositions. It is noted that no specific drug is claimed in the claims in question. The aqueous solubility ratio is an inherent property of a drug and since no specific drug is recited in claims 1 and 15, the prior art renders claim 53 obvious or meets claim 53.

There is no demonstration in applicants' specification that the recited particle sizes provide unusual results. In the absence of a showing the particles having the recited particle sizes in claims 23 and 26 is not patentable over particles of the prior art. Regarding claim 38, Miyajima's disclosure of nifedipine as poorly water-soluble drug whose solubility can be improved would motivate a person of ordinary skill in the art to prepare a product containing nifedipine in order to improve the solubility. Miyajima prepares the solid dispersion by spray drying and applicants form the molecular dispersion by spray drying. Thus the dispersion of Miyajima formed by spray drying is molecularly dispersed.

While Miyajima discloses in the background the possibility of converting nicardipine hydrochloride into an amorphous type (column 1, lines 48 and 49), Miyajima does not specifically use the words "amorphous dispersions." However, since Miyajima discloses spray drying, even if it is just once, and since the instant invention prepares amorphous dispersions by spray drying, then Miyajima' product would be amorphous. Miyajima does not also state that the product is crystalline.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the product of Miyajima by spray drying with the expectation of having solid amorphous dispersion.

Response to Arguments

8. Applicant's arguments filed 10/17/06 have been fully considered but they are not persuasive.

Applicant argue that Miyajima mentions the phrase "spray drying" only once in the entire disclosure and that spray drying does not necessarily produce amorphous drug, that the Remington article bears witness b) that the declaration of Scott B. McCray demonstrates that granulation according to Miyajima does not form homogenous solid amorphous dispersion.

Response:

The Remington reference does state that spray drying leads to "crystals and/or amorphous solids depending on the rate and conditions of solvent removal." Thus, the Remington reference further supports the fact that spray drying leads to amorphous products. It is respectfully noted that the invention is directed to a composition and a composition that is formed by spray drying.

Applicants appear to imply that the spray dried product of Miyajima may or may not be amorphous, and if this is the case, it may also raise the question whether applicants product is amorphous since the claimed product is formed/prepared by spray drying. Although, applicants argue that Miyajima mentions spray drying only once in the disclosure and as such cannot be relied upon for spray drying, it is the Examiner's position that there is a disclosure of spray drying in Miyajima. The claims are composition claims. Also, the recitation of spray-dried particles solidifying in less than 5 seconds is an inherent characteristic of the spray drying process. However, both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Miyajima solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by spray drying as does the claimed invention differs in any way from the claimed solid dispersion.

Examiner recognizes that combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion can only establish obviousness, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is suggestion in Miyajima that the solubility of nifedipine, a poorly water-soluble drug, can be improved and Miyajima provides the how to process for improving drugs that are sparingly soluble.

The Declaration: By Scott B. McCray

The declaration is not commensurate with the claims and even with the disclosure of Miyajima as it relates to spray drying. Miyajima specification contemplates the use of spray drying technique for removing the solvent to arrive at the final product. The declaration is centered on granulation, which is not the claimed invention and which is not one of the steps contemplated by Miyajima (see column 3, lines 57 and 58).

Response: The claimed invention in 1 is directed a composition comprising sparingly soluble water soluble drug and HPMCAS. The dose to aqueous solubility ratio of greater than 100 ml is a property of the drug or composition. Thus the declaration is not commensurate with the claims. It is respectfully noted that no specific drug is claimed in the rejected claims. Any sparingly water-soluble drug may have this property.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

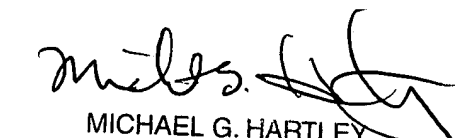
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Blessing Fubara
Patent Examiner
Tech. Center 1600



MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER